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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,117	11/06/2000	Jon A. Wolff	Mirus.018.02	8189

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1633	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,117	WOLFF ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Specification

The description of the drawings should read "FIG. 2A-2C" (page 4, line 14) and "FIG. 3A-3C" (page 4, line 20).

Page 3, line 32, is confusing because of the word "ore".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a marker protein operably linked to a promoter and wherein said marker protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for the methods

claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 39 encompasses injecting any blood vessel with any polynucleotide, using any method of immunosuppression and any method of impeding blood flow such that polynucleotide is delivered to any cell. Claim 1 requires delivery to any parenchymal cell. Claim 5 requires delivery to any muscle cell. Claims 6-31 require delivery to muscle cells of limbs, some of which require delivery to specific muscles within the limbs.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under

Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The specification teaches administering naked plasmid DNA encoding a marker protein to an artery of the arm or leg and obtaining expression in muscle cells of the arm or leg, respectively. However, Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, page 2197-2203) taught administering adenoviral particles to a femoral artery and vein occluded using a tourniquet. The adenoviral vector encoded LacZ which was expressed in hepatocytes but not in muscle cells of the limb (page 2201, col. 2, 2nd para.). Ye (March 1, 2000, Human Gene Therapy, Vol. 11, pages 621-627) taught administering adenoviral particles encoding LacZ to the portal vein/artery occluded with clamps and obtaining expression in kidney, liver and spleen but not in skeletal muscle or heart. The specification does not teach targeting any parenchymal cell other than skeletal muscle cells. The specification does not teach delivering DNA to a non-leg or non-arm blood vessel and expressing the DNA in leg or arm skeletal muscle. For example, the

specification does not teach delivering DNA to a blood vessel in the leg and obtaining expression in muscle cells of the arm.

Because of the lack of clarity regarding "externally impeding *in vivo* blood flow," "applying immunosuppression," the methods of delivery in claims 1, 3-35, 37-41 encompass the method of delivery taught Milas and the methods of delivery in claims 1, 3-32 and 37-41 encompass the method of delivery taught by Ye. However, the method of delivery taught by Milas or Ye cannot result in delivery to muscle cells of the limb as in claims 6-31. Therefore, claims 6-31 should not encompass methods of delivery taught by Milas and Ye.

Beyond that, it cannot be determined how targeting a cell as broadly claimed is effected by the location of the blood vessel injected, the type of polynucleotide (adenovirus vs. naked plasmid DNA), the method of occlusion (tourniquet vs. clamps, balloon catheter), or the method of immunosuppressing (administering vs. not administering an immunosuppressive agent). Specifically, the requirements for targeting muscle cells within the limb cannot be determined. Clarification is required.

In particular, the specification does not provide adequate guidance for one of skill to determine why or when an immunosuppressive agent is administered, how administering such an agent effects the delivery of DNA or whether different immunosuppressive agents have different effects on the delivery of DNA. Nor can it be determined why one of skill would want to perform the method in an immunosuppressed mammal (SCID mouse, nude mouse, HIV infected human, etc.; see 112/2nd) which is also encompassed by the claims. Clarification is required.

The specification does not enable delivering any polynucleotide as broadly claimed. The specification only teaches delivering DNA encoding a marker protein operably linked to a promoter. The specification does not enable delivering any other polynucleotide or delivering DNA encoding a marker protein in the absence of a promoter. The specification does not enable one of skill to determine "blocking polynuceotides for preventing gene expression."

The specification does not provide an enabled use for mere delivery of a polynucleotide to a cell. For the delivery to have an enabled use, it must encode a protein which is expressed to detectable levels in the cell. Therefore, the claims should recite a final step of obtaining detectable levels of expression of the protein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 39 are indefinite for the following reasons:

The limitations in d) (claim 1) or c) (claim 39) are unclear because they may be a result of the previous steps or may be a new step in addition to the previous steps. Clarification is required.

Step a) is unclear because it does not require the blood vessel is part of the mammal.

Step b) is unclear because it does not require the blood flow to be impeded within the mammal or within the blood vessel receiving the polynucleotide.

Step b) is unclear because the metes and bounds of what applicants consider "externally impeding" blood flow cannot be determined. External is a relative term; it cannot be determined if it refer to the blood vessel being impeded, blood vessels in general or the mammal. Are clamps encompassed by the claim, as they are "external" to the mammal and impede blood flow? How would "externally impeding" blood flow compare to "internally impeding" blood flow?

Step c) is unclear because the metes and bounds of what applicants consider "applying immunosuppression" cannot be determined. An immunosuppressive compound may be administered, immunosuppression may be induced by radiation, and immunosuppression may be caused by viruses; the immune system may be suppressed in an area by occluding a blood vessel and preventing blood cells from contacting that area. It is unclear whether any or all of these methods relate to "applying immunosuppression."

Claims 1 and 39 do not recite all the steps of the method because the mere delivery of polynucleotides to cells does not have a disclosed use. The method should result in expression of a protein in a cell.

Claim 4 is indefinite because the metes and bounds of a "blocking polynucleotide" for preventing gene expression cannot be determined. Are they polynucleotides encoding proteins that block gene expression or are they antisene/ribozymes? If applicants intend the claim to mean antisense or ribozymes, such embodiments a restriction requirement will be set forth.

Claims 8, 9, 10, 26, 29 are indefinite because "anterior" is relative to the mammal and the orientation of the mammal; therefore, the metes and bounds of an "anterior muscle cell" cannot be determined. For example, is a muscle cell in the palm of the hand an anterior muscle cell? If a mouse is walking, is a muscle cell on a mouse's head near the neck an anterior muscle cell? Such a cell would be on top of the mouse, not on the back of the mouse because a mouse walks on all four. The line within a muscle demarcating the anterior and posterior of a particular muscle within a mammal cannot be determined. If the mammal were bisected, front and back, are only cells in the back anterior? Or if the muscle itself were bisected, front and back, are only the cells in back are considered "anterior"? Is "tibialis anterior" the name of a muscle or a relative term (claim 29)?

Likewise, claims 13-15, 21-23 and 25 are indefinite because "posterior" is relative to the mammal and the orientation of the mammal; therefore, the metes and bounds of an "anterior muscle cell" cannot be determined. Is "tibialis posterior" the name of a muscle or a relative term (claim 25)?

Claims 9, 14, 22, 24, are indefinite because the term "superficial" is relative; therefore, the metes and bounds of a "superficial" muscle cell cannot be determined. How much toward the surface must a cell be to be considered superficial?

Likewise, the metes and bounds of what applicants consider a "deep" muscle cell or an "internal" muscle cell cannot be determined (claims 23, 25 and 27300). How deep is "deep"? All muscles are "internal" as they are not on the outside of the skin. Thus, the metes and bounds

of "deep" and "internal" muscle cells cannot be determined. Furthermore, the boundary between "superficial" and "internal" or "deep" muscle cells cannot be envisioned, and the distinction between "internal" and "deep" muscle cells cannot be determined.

The term "interior" blood flow (claim 32) lacks antecedent basis and the metes and bounds of the term cannot be determined. All blood vessels within the mammal are inside the mammal. Thus, it cannot be determined to which blood vessel applicants are referring.

The notation "spf." and "prof." is unclear because it cannot be determined what the abbreviations mean (claims 11 and 12).

The metes and bounds of "externally impeding" blood flow (claim 32) cannot be determined. External is a relative term; it cannot be determined if it refer to the blood vessel being impeded, blood vessels in general or the mammal. Are clamps encompassed by the claim, as they are "external" to the mammal and impede blood flow? How would "externally impeding" blood flow compare to "internally impeding" blood flow?

The phrase "externally applying pressure" (claims 32, 33) to blood vessels is indefinite as the metes and bounds of what methods are encompassed by the claims cannot be determined. Does "external" imply something must be applied to the outside of the mammal or just outside the blood vessel? Does it encompass any "external" force that increases blood pressure, e.g. drugs? Clarification is required.

Claim 32 is indefinite because it is unclear. As written, the "pressure" may not be applied to the blood vessel that receives the polynucleotide. As such, the claim encompasses applying

pressure to any blood vessel and impeding blood flow of a specific blood vessel, e.g. tieing a string around your finger and impeding blood flow in an arm vein. There should be a nexus between impeding blood flow of a blood vessel and applying pressure to that blood vessel.

The metes and bounds of what applicants consider "compressing" skin cannot be determined (33-36). Is pinching the skin encompassed by the claim? If the polynucleotide is injected in the arm, does the claim encompass "compressing" the skin of the foot? There should be a nexus between impeding blood flow of a blood vessel and applying pressure to that blood vessel by "compressing" skin. Similarly, there should be a nexus between impeding blood flow of a blood vessel and applying pressure to that blood vessel using a tourniquet, cuff or sphygmomanometer.

Claims 34-36 are indefinite because a tourniquet or cuff is not "applied" "over the skin". A tourniquet or cuff is placed on an arm, leg, etc. Pressure may be applied to a blood vessel using a tourniquet or cuff. But a tourniquet or cuff is not "applied" "over the skin".

The metes and bounds of "cuff" (claims 35, 36) cannot be determined. The term does not have a defined meaning in the art. The specification defines "cuff" as a devise for impeding blood flow in a blood vessel (page 5, line 13). While a sphygmomanometer cuff can be envisioned, and the specification states tourniquets are "cuffs," other cuffs cannot be envisioned. Thus, the metes and bounds of devises encompassed by the term "cuff" cannot be determined. Does the cuff have to be applied to the outside of the mammal or is a string around the blood vessel a cuff? The definition provided in the specification is confusing. Is a cuff a "device for

impeding blood flow through mammalian internal blood vessels" (line 13) or a "device applied to exterior to the mammal's skin and touches the skin in a non-invasive manner" (line 14)? It cannot be determined which definition is to be applied. Therefore, the metes and bounds of the term cannot be determined.

The metes and bounds of "primarily" (claim 37) cannot be determined. Does the term mean greater than 50% or does it mean the greatest percentage? Deletion of the term is recommended.

The metes and bounds of non-vascular parenchymal cells cannot be determined. The specification and the art do not define the parenchymal cells of vascular tissue; therefore, the metes and bounds of non-vascular parenchymal cells cannot be determined. What are the distinguishing cells of a blood vessel as implied on page 10, line 1?

Claim 39 is indefinite because the metes and bounds of "full function" of a limb cannot be determined. Is full function limited to motor function, blood vessel function or neurological function or is it limited to the function of the limb itself? Is full function a relative term used to compare the function of a limb before and after treatment. Full function could encompass a limb having motor function, blood vessel function and neurological function after treatment, wherein the motor skills are impaired. Clarification is required.

Claim 39 is indefinite because "subsequent to delivery" is unclear. Does the phrase refer to delivery of the polynucleotide, the immunosuppressive agent or the pressure increasing agent?

Claim 40 is indefinite because the metes and bounds of "continuous" treatment is unclear. Does the term mean the treatment is constantly going into the mammal or the treatment is given on a regular basis for a period of time? If it is given on a regular basis for a period of time, how long is it given? Is treatment once a day for 5 days "continuous"? Is treatment once a day for the lifetime of mammal continuous?

Claim 41 is indefinite because the metes and bounds of the term transient treatment cannot be determined. How long is the treatment given? How long is the treatment not given? Is treatment once a day "transient" if the treatment maintains immunosuppression?

Claim 42 is indefinite because the genus/species relationship of the term "immunosuppression" with the Markush group is not commensurate in scope. Immunosuppression is a method that causes suppression of the immune system while "oral treatment" and "subcutaneous injection" are routes of administering an agent. Immunosuppression may be performed using an "oral treatment" or "subcutaneous injection". An immunosuppressive agent may be delivered orally or subcutaneously. However, immunosuppression is not an "oral treatment" or "subcutaneous injection."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 3, 4, 5, 32-35, 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Milas taught administering adenoviral particles to an occluded femoral artery and vein of a rat. The femoral artery and vein were occluded using a tourniquet. The adenoviral vector encoded LacZ which was expressed in hepatocytes; hepatocytes are parenchymal cells. The limitation of "applying immunosuppression" is equivalent to occluding the blood vessels - the area of occlusion is immunosuppressed because blood cells are prevented from flowing through that area.

Claim 4 is included because the metes and bounds of "blocking polynucleotide" cannot be determined and the phrase "for preventing gene expression" is an intended use and may not occur. Claim 5 is included because the method of Milas inherently results in expression in smooth muscle cells of the blood vessel. The "immunosuppression" is "continuous" (claim 40) because it continues throughout the operation. The "immunosuppression" is "transient" (claim 41) because it does not continue throughout the life of the rat.

4. Claim 1, 3-32 and 37-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Sferra (April 10, 1997, Human Gene Therapy, Vol. 8, pages 681-687).

Sferra taught administering adenoviral particles to an occluded superior mesenteric artery and vein of a rat. The artery and vein were occluded using a clamp. The adenoviral vector encoded LacZ which was expressed near the serosa and mucosa of the intestines, specifically the

muscular cells (page 683, Fig. 1, Fig. 2; page 684, para. bridging col. 1 and 2; para. bridging pages 684-685).

It is unclear how the muscle cells of the intestines correlate to "interior," "anterior," "deep," posterior," or "superficial" muscle cells as claimed as in cannot be determined where the cells were in relationship to the rat.

The method of Sferra differs from the teachings disclosed in the instant application only in the use of clamps rather than a tourniquet, both of which cause occlusion of the blood vessel. Sferra states one animal had expression outside the liver and intestines. Therefore, without evidence to the contrary, the method of Sferra inherently results in expression in muscle cells of the leg and arm as claimed (claims 6-31).

The limitation of "applying immunosuppression" is equivalent to occluding the blood vessels - the area of occlusion is immunosuppressed because blood cells are prevented from flowing through that area.

Claim 4 is included because the metes and bounds of "blocking polynucleotide" cannot be determined and the phrase "for preventing gene expression" is an intended use and may not occur. Claim 37 is included because it cannot be determined whether the method of Sferra results in delivery "primarily" to limb cells. The "immunosuppression" is "continuous" (claim 40) because it continues throughout the operation. The "immunosuppression" is "transient" (claim 41) because it does not continue throughout the life of the rat.

5. Claims 1-5, 8-10, 13-15, 32, 38-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolff (US Patent 5,693,622 Dec. 2, 1997).

Wolff taught administering naked plasmid DNA encoding marker protein into the interstitium of the heart of a nude rat in an amount sufficient to obtain marker protein expression in cardiocytes (col. 47, line 16-41).

Administering DNA into the interstitium is equivalent to introducing DNA into a blood vessel as claimed - the interstitium of the heart is the area between the pericardium and the heart and is a "blood vessel" because it is a vessel that contains the heart and contains blood because the heart contains blood.

Injection into the interstitial space of the heart is equivalent to "externally impeding blood flow" as claimed because the method inherently increases pressure in the area of injection which impedes blood flow and because the needle used is external to the heart.

Nude rats have immunosuppression "applied" "continuously" because they are permanently immunosuppressed.

Claim 4 is included because the metes and bounds of "blocking polynucleotide" cannot be determined and the phrase "for preventing gene expression" is an intended use and may not occur.

6. Claims 1-32 and 37-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Nabel (U.S. Patent, 5,910,488 filed 1-1-95).

Nabel ('488) taught pre-treating a mammal with cytoxan to eliminate suppressor T-cells, delivering naked plasmid DNA encoding HLA-B7 using an occlusion balloon catheter and obtaining antibodies against HLA-B7 (col. 15, lines 21-26; col. 25, lines 52-67; col. 26, lines 52-col. 28, line 4).

Antibody production is an indication that the vector has been delivered to a lymphocyte which is a parenchymal cell of the immune system. It is noted claim 39 does not require the cell be a parenchymal cell.

The method of Nabel differs from the teachings disclosed in the instant application only in the use of a balloon catheter rather than a tourniquet, both of which cause occlusion of the blood vessel. Therefore, without evidence to the contrary, the method of Nabel inherently results in expression in muscle cells as claimed (claims 5-31).

Claim 4 is included because the metes and bounds of "blocking polynucleotide" cannot be determined and the phrase "for preventing gene expression" is an intended use and may not occur. Claim 37 is included because it cannot be determined whether the method of Nabel results in delivery "primarily" to limb cells. Claims 40 and 41 are included because it cannot be determined what applicants considered "continuously" or "transiently."

7. Claim 1-32 and 37-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Nabel (U.S. Patent, 5,698,531, filed 1-23-95).

Nabel ('531) taught injecting naked plasmid DNA into a blood vessel that was occluded using a balloon catheter and obtaining marker protein expression in smooth muscle cells surrounding blood vessels (claim 1).

The limitation of "applying immunosuppression" is equivalent to occluding the blood vessels - the area of occlusion is immunosuppressed because blood cells are prevented from flowing through that area.

Smooth muscle cells are parenchymal cells of the blood vessel because they provide an essential function to the blood vessel: the ability to constrict. It is unclear how the smooth muscle cells correlate to "interior," "anterior," "deep," posterior," or "superficial" muscle cells as claimed as in cannot be determined where the cells were in relationship to the rat (see 112/2nd). In addition, Nabel taught the method results in transfecting parenchymal cells (col. 4, line 16). The method of Nabel requires a balloon catheter while the instant application uses a tourniquet, both of which cause occlusion of the blood vessel and expression in muscle cells. Therefore, without evidence to the contrary, the method of Nabel inherently results in expression in leg and arm muscles and the muscles in claims 11, 12, 16, 17, 24, 25, 29-31, as claimed.

Claim 4 is included because the metes and bounds of "blocking polynucleotide" cannot be determined and the phrase "for preventing gene expression" is an intended use and may not occur. Claim 37 is included because it cannot be determined whether the method of Nabel results in delivery "primarily" to limb cells. The "immunosuppression" is "continuous" (claim

40) because it continues throughout the operation. The "immunosuppression" is "transient" (claim 41) because it does not continue throughout the life of the rat.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER